Atypical Phenotypes in Classical Hodgkin Lymphoma

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KEYWORDS

• Immunohistochemistry • CD30 • CD15 • PAX-5 • CD45 • CD20 • CD79a • OCT-2 • BOB.1

KEY POINTS

- Most cases of classical Hodgkin lymphoma have a characteristic phenotype, with expression of CD30, CD15, and PAX-5, and absence of CD45 and most B-lineage markers.
- A significant subset of cases of classical Hodgkin lymphoma has atypical phenotypes, usually absence of CD15 or expression of one or more B-lineage markers, such as CD20, CD79a, OCT-2, and BOB.1.
- The most common problems in the immunodiagnosis of classical Hodgkin lymphoma involve the misidentification of other cells types, such as immunoblasts or histiocytes, as Hodgkin cells, or the inability to assess multiple antigens in small tissue biopsies.
- Cases expressing the full B-cell program may represent a borderline lymphoma intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma.
- Novel multiplexing technologies may help provide better assessment of antigen expression on Hodgkin cells.

ABSTRACT

Classical Hodgkin lymphoma has a characteristic immunophenotype in most cases, with expression of CD30, CD15, and PAX-5, and absence of CD45 and T-lineage markers. However, in a significant subset of cases, atypical staining patterns may be seen for one or more antigens, particularly negative staining for CD15 or staining for one or more B-lineage markers, such as CD20, CD79a, OCT-2, or BOB.1. The greatest pitfall is in the misinterpretation of other cells, such as immunoblasts or histiocytes, as Hodgkin cells.

OVERVIEW

Classical Hodgkin lymphoma is diagnosed by the identification of Reed-Sternberg cells and variants (collectively Hodgkin cells) in the appropriate cellular milieu. This was previously accomplished using solely morphologic criteria. The development of effective immunohistochemical studies that can be performed in formalin-fixed and paraffin-embedded sections, along with the availability of antibodies reactive on formalin-resistant epitopes, has allowed a more accurate immunohistochemical recognition of Hodgkin cells, with the realization that many cases previously regarded as classical Hodgkin lymphoma actually represented other entities, such as T-cell/histiocyte-rich large B-cell lymphoma. The purpose of this article was to review the immunophenotypes that may be observed in classical Hodgkin lymphoma.

The typical phenotype observed in Hodgkin lymphoma is shown in **Table 1**. CD30 is the most consistent of the major diagnostic markers of Hodgkin cells, expressed in virtually 100% of cases. The older literature suggested a lower incidence of CD30 expression, on the order of 90% of cases, probably as a reflection of the results obtained before the current era of optimal antigen retrieval.[1] The staining pattern for CD30

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Table 1
Immunophenotype of Hodgkin cells in classical Hodgkin lymphoma

CD30	100%
CD15	70%
PAX-5	95%
CD45	5%
CD20	25%
CD79a	15%
BOB.1	15%–25%
OCT-2	15%–50%
MUM-1	100%
Fascin	100%
EMA	5%
EBER/EBV-LMP-1	30%
BCL2	25%
BCL6	15%
CD138	40%
CD10	0%
CD3, other T-lineage	0%

is membranous and/or paranuclear, as well as weaker diffuse cytoplasmic; however, diffuse cytoplasmic staining alone is nonspecific (**Fig. 1**). It is controversial whether Hodgkin cells are truly ever CD30-negative or whether the negativity is a technical artifact, although I believe that I have rarely seen cases of classical Hodgkin lymphoma that were truly CD30-negative. CD30 remains expressed, even after anti-CD30 therapy.[2] CD15 is a less-consistent marker of Hodgkin cells, expressed in the literature in about 85% of cases.[3] Again, the staining is membranous and/or paranuclear, with a nonspecific diffuse granular cytoplasmic staining (the latter may frequently be seen in peripheral T-cell lymphoma) (**Fig. 2**). In my recent personal experience, the percentage of CD15 positivity is much lower than 85%, probably less than 50%. Although much of that difference can be explained by referral pattern, specifically the tendency of pathologists to refer CD15-negative cases for expert consultation, I still believe that the true percentage of CD15 positivity in classical Hodgkin lymphoma is well below 85% and probably closer to 70%. I attribute most of the lower positivity (even in the advent of more effective immunohistochemical technology) to the greater recognition of CD15 positivity in histiocytes and other cell types that can mimic CD15 expression in Hodgkin cells. It is now well recognized that histiocytes may show a granular cytoplasmic positivity for CD15 that is concentrated in the paranuclear region, and that neoplastic T cells may also show a granular pattern of cytoplasmic CD15 reactivity.

PAX-5 is another consistent marker of Hodgkin cells, evidence of the derivation of Hodgkin cells from the B-cell lineage. The most comprehensive studies have reported PAX-5 expression in approximately 95% of cases.[4] In addition, the expression is consistently weak to moderate in intensity, in contrast to the consistently strong

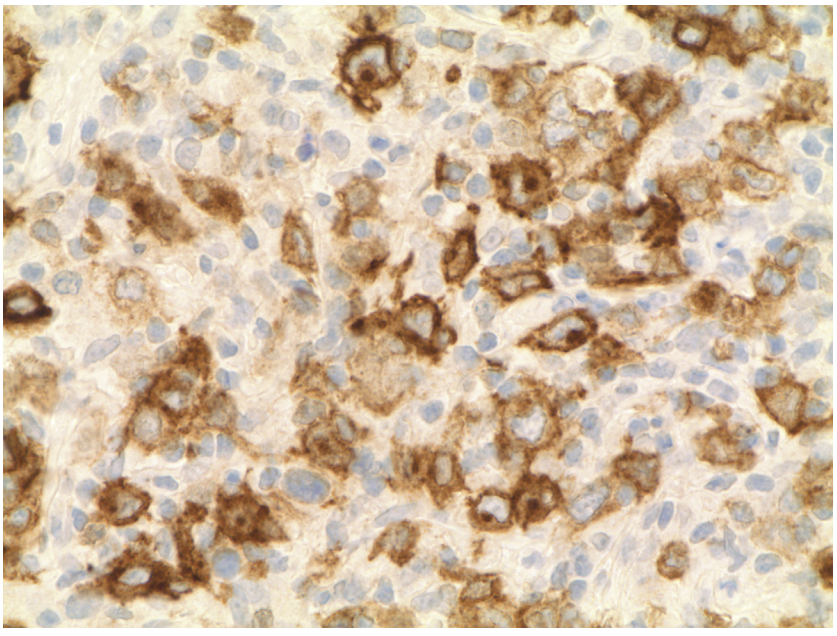

Fig. 1. CD30 in classical Hodgkin lymphoma. Membrane and/or paranuclear staining is evidence of true CD30 staining. Cytoplasmic staining alone lacks specificity.